

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-fjs.com

ORIGINAL ARTICLE

Factors influencing contralateral neck metastasis in oral squamous cell carcinoma

Tzu-Chieh Lin ^{a,†}, Yung-An Tsou ^{b,c,d,†}, Da-Tian Bau ^d, Ming-Hsui Tsai ^{b,c,d,*}

^a Department of Otolaryngology, China Medical University Beigang Hospital, Taiwan

^b Department of Otolaryngology, China Medical University Hospital, Taichung, Taiwan

^c Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

^d Terry Fox Cancer Research Lab, China Medical University Hospital, Taichung, Taiwan

Received 28 November 2011; received in revised form 12 January 2012; accepted 8 April 2012

Available online 7 June 2012

KEYWORDS

contralateral;
metastasis;
neck;
squamous cell
carcinoma

Summary *Background:* Neck lymph node metastasis is the most critical factor influencing survival and prognosis of oral squamous cell carcinoma (OSCC). The risk factors for contralateral neck metastasis are still controversial.

Purpose: To identify the risk factors of contralateral neck metastasis of OSCC.

Methods: The 683 previously untreated OSCC patients managed at the China Medical University Hospital from January 1997 to December 2006 were reviewed. We statically analyzed the risk factors potentially related to contralateral neck lymph node metastasis.

Results: Mouth floor invasion and midline crossing tumors were statistically significant for the presence of pretreatment cN2c. Midline-crossing tumors had statistically significant impact on the presence of pathologic contralateral neck lymph node metastasis (pN2c). Mouth floor invasion and poorly differentiated tumor showed statistically significant impact on contralateral neck relapse for OSCC patients who underwent only ipsilateral neck dissection. Poorly differentiated tumor showed statistically significant impact on contralateral neck relapse for patients with contralateral neck dissection.

Conclusion: Mouth floor invasion, midline crossing tumors, poorly differentiated tumors had a high risk in contralateral neck metastasis.

Copyright © 2012, Taiwan Surgical Association. Published by Elsevier Taiwan LLC. All rights reserved.

* Corresponding author. 2 Yuh-Der Rd, Taichung City 404, Taiwan.

E-mail address: d22052121@yahoo.com.tw (M.-H. Tsai).

† Tzu-Chieh Lin and Yung-An Tsou are equally contributors to this work.

1. Introduction

Neck lymph node metastasis is the most significant prognostic and survival factor in patients with oral squamous cell carcinoma (OSCC).¹ Patients with pathologically negative cervical lymph nodes are believed to have a relatively good prognosis. In contrast, the outcome of patients with lymph node metastasis occurring after excision or radiotherapy of the primary tumor is poor.² Factors that predict contralateral lymph node metastasis in OSCC patients remain controversial. Predicting contralateral neck metastasis may improve the prognosis of these patients. This study was aimed to examine possible predictive clinicopathologic factors for contralateral neck metastasis in surgically-treated primary OSCC.

2. Setting and ethics

This study was held in the tertiary referral hospital [China Medical University Hospital (CMUH), head and neck cancer center] in Taiwan. Ethical approval was granted by the institutional review board, CMUH, Taichung, Taiwan.

3. Patients and methods

A total of 683 previously untreated OSCC patients managed at the CMUH from January 1997 to December 2006 were reviewed. The tumor was staged in accordance with the American Joint Committee on Cancer sixth edition TNM Staging Classification. All patients were treated with surgery with or without adjuvant therapy. The inclusion criteria were as follows: (1) patients with biopsy-confirmed diagnosis of SCC of the oral tongue, buccal mucosa, gum, palate, and mouth floor; (2) patients not previously submitted for treatment; and (3) patients for curative surgery as first treatment. The exclusion criteria included at least one of the following: (1) contraindication for surgery; (2) distant metastasis at the time of admission; (3) presence of other simultaneous primary tumors; and (4) patients who refused surgical treatment.

Selective neck dissection I-III was performed on all T2-4 tumors without presence of clinically positive nodal disease, while selective neck dissection I-V was performed in the presence of clinically positive nodal disease. Whether the tumor crossed the midline or there was floor of the mouth invasion was decided via a computed tomography scan and physical examination. Postoperative adjuvant therapy was applied to patients with either one of the major risk factors (i.e., close or positive section margin or extracapsular spread) or more than two minor risk factors (i.e., perineural invasion, lympho-vascular permeation, $\geq N2$, $\geq T3$). The kind of postoperative adjuvant therapy was chosen via the Radiotherapy-Oncology-Head and Neck Surgery Combined Conference according to the criteria of CMUH. All patients were followed-up at least for 24 months or until death and they were all retrospectively reviewed under the Institutional Review Board approval of the China Medical University Hospital.

4. Statistical analysis

Multivariate and univariate logistic regression analysis combined with stepwise selection techniques was used to examine the predictive clinicopathologic factors for contralateral neck metastasis. A $p < 0.05$ was considered statistically significant. Age, sex, tumor site, primary tumor laterality, TNM status, clinical N status, pathologic T status, ipsilateral pathologic N status, tumor stage, status of residual disease, histopathologic differentiation, adjuvant therapy, local relapse, extra-capsular spread by lymph node metastasis, perineural/lympho-vascular invasion, and type of adjuvant therapy were evaluated for association with contralateral neck metastasis. Survival curves were calculated by the Kaplan-Meier method with log rank analysis.

Clinical and pathologic variables were evaluated via the predictive value (univariate) for the occurrence of metastasis in the contralateral lymph nodes. The odds ratio was the association measurement used to evaluate metastases by each factor under study. Multivariate analysis, followed by stepwise selection, was conducted after adjusting for the effect by dummy variables, to verify the maintenance of such variables for risks of metastasis.

5. Results

Of the 683 patients with SCC of the oral cavity who fulfilled the inclusion criteria, 624 were male and 356 were aged ≥ 50 years. The primary tumor location was on the oral tongue in 298 patients (43.6%), buccal mucosa in 283 (41.4%), gums in 46 (6.7%), lips in 24 (3.5%), mouth floor in 19 (2.8%), and on the palate in 13 (1.9%). There were seven pretreatment cN2c patients.

Mouth floor invasion and midline crossing tumors were statistically significant for the presence of pretreatment cN2c after statistical analysis (Table 1). All seven cN2c patients underwent bilateral neck dissection. Five of them were further confirmed by pathology as bilateral neck metastasis (pN2c). Another patient had contralateral neck relapse later. Of the 677 non-cN2c patients, 48 underwent prophylactic bilateral neck dissection. Post-operatively, 8 of the 48 elective bilateral neck dissection were pathologically further diagnosed to have bilateral neck lymph node metastasis (pN2c).

There were 13 pathologic N2c cases. After statistical analysis, midline-crossing tumors had statistically significant impact on the presence of pathologic contralateral neck lymph node metastasis (pN2c; Table 1). Contralateral neck relapse was diagnosed in 26 patients, one of whom was previously diagnosed as a case of cN2c and underwent bilateral neck dissection. Eighteen of the 26 cases underwent ipsilateral neck dissection for curative therapy, while seven had a wait-and-see policy for their neck nodes (Fig. 1).

Mouth floor invasion and poor differentiation of tumor showed statistically significant impact on contralateral neck relapse for oral SCC patients who received ipsilateral neck dissection. Poorly differentiated tumor showed statistically significant impact on contralateral neck relapse (Table 2).

Table 1 Risk factors for the presence of cN2c and pN2c. Data are expressed as odds ratio (95% confidence interval).

Variable	Category	cN (n = 7)		pN (n = 13)	
		Univariate	Multivariate	Univariate	Multivariate
Age	≤50	1.0		1.0	
	>50	1.2 (0.3,5.5)		1.8 (0.4, 8)	
cT stage	cT1,cT2	1.0	1.0	1.0	
	cT3,cT4	11.6 (1.4,97.2)*	4.7 (0.5,43.0)	22 (0.1, 129)	
pT stage	pT1,pT2			1.0	
	pT3,pT4			5.7 (0.6, 49.7)	
cN stage	cN0			1.0	
	≥cN1			1.3 (0.2, 7.1)	
Mouth floor invasion	No	1.0	1.0	1.0	
	Yes	52.9 (6.3,446.3)#	12.4 (1.2,124.5)*	5.4 (1, 30.2)	
Cross-midline tumor	No	1.0	1.0	1.0	1.0
	Yes	52.9 (6.3,446.3)#	13.1 (1.3,130.9)*	6.0 (1.1, 33.4)*	6.0 (1.1,33.4)*
Tongue base invasion	No			1.0	
	Yes			0.3 (0.3, 79.1)	
Tumor differentiation	Well/Moderate			1.0	1.0
	Poor			5.3 (0.6, 47)	3.7 (0.8, 30.7)
Extracapsular spreading	No			1.0	1.0
	Yes			6.4 (0.7, 56.3)	3.3 (0.6, 8.1)
Perineural invasion	No			1.0	1.0
	Yes			1.7 (0.4, 7.7)	3.4 (1.4, 30.2)
Lymphovascular permeation	No			1.0	1.0
	Yes			4(0.6, 29.2)	5.0(1.5, 8.4)

* = $p < 0.05$; # = $p < 0.01$.

With regard to survival results, patients with contralateral neck relapse had poorer outcomes. Advanced OSCC patients initially presenting with mouth floor invasion or tumor with midline crossing who underwent contralateral neck treatment had better outcomes. Patients with advanced poorly differentiated OSCC had better survival outcomes if they underwent contralateral neck dissection initially. There was no survival benefit for advanced OSCC with perineural invasion or lympho-vascular permeation if they initially underwent contralateral neck dissection.

The odds ratio was the association measurement used to evaluate metastases in accordance with each factor under study. By multivariate analysis, tumor with invasion to the mouth floor exhibited a 12.4-fold higher risk of association

with cN2c, while midline-crossing tumor showed a 13.1-fold higher risk of association with cN2c (Table 2). Midline-crossing tumors exhibited a 6.0-fold higher risk of association with pN2c by multivariate analysis (Table 1).

For cases with contralateral neck dissection, poorly differentiated tumors exhibited a 3.9-fold higher risk of contralateral neck relapse by multivariate analysis (Table 2). In patients with ipsilateral neck dissection, mouth floor invasion showed a 4.9-fold higher risk of contralateral neck relapse, while poorly differentiated tumors showed an 8.0-fold higher risk by multivariate analysis (Table 2).

In this study, considering 13 cases of pathology-confirmed contralateral neck metastasis from 55 cases of contralateral neck dissection and the 25 relapse cases from 628 observation cases of the contralateral neck, the frequency of contralateral neck metastasis and occult contralateral neck metastasis was 5.6% (38/683) and 4.9% (33/676), respectively.

6. Discussion

A review of related articles shows that the frequency of metastasis to contralateral cervical lymph nodes of oral carcinomas varies from 4% to 16.1%.¹⁻⁸ The definition of contralateral neck metastasis includes the presence of initial contralateral lymph node involvement, occult contralateral neck lymph node metastasis confirmed via pathology study, and contralateral neck relapse. In this study, the frequency for contralateral neck metastasis and occult contralateral neck metastasis was 5.6% (38/683) and 4.9% (33/676), respectively.

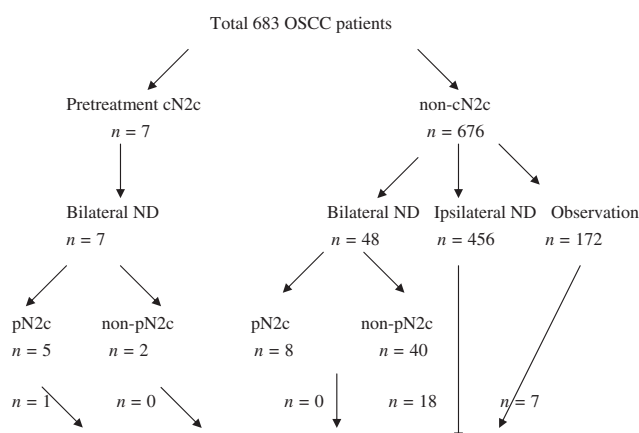
**Figure 1** Contralateral neck relapse.

Table 2 Risk factors of contralateral neck relapse in the three groups*, by multivariate analysis. Data are expressed as odds ratio (95% confidence interval).

Variables	Category	Contralateral neck dissection (n = 55)	Without contralateral neck dissection (n = 628)	Ipsilateral neck dissection (n = 711)
Mouth floor invasion	No	1.0	1.0	1.0
	Yes	2.7 (0.8, 9.2)	3.5 (1.0, 12.5)	4.9 (1.2, 21.0)*
Cross-midline tumor	No	1.0	1.0	1.0
	Yes	1.9 (0.5, 6.8)	2.0 (0.5, 7.8)	1.5 (0.3, 8.6)
Tongue base invasion	No	1.0	1.0	1.0
	Yes	2.9 (0.8, 11.0)	2.7 (0.6, 11.6)	3.5 (0.8, 16.1)
Tumor differentiation	Well/moderate	1.0	1.0	1.0
	Poor	3.9 (1.2, 12.8)*	3.3 (1.4, 11.1)*	8.0 (1.5, 43.5)*
Perineural invasion	No	1.0	1.0	1.0
	Yes	1.5 (0.5, 4.3)	1.6 (0.5, 5.1)	0.8 (0.2, 2.8)
Lymphovascular permeation	No	1.0	1.0	1.0
	Yes	2.4 (0.8, 7.8)	3.2 (0.9, 11.0)	3.7 (1.0, 13.8)

Contralateral neck dissection: patient who received contralateral neck dissection; without contralateral neck dissection: there was no contralateral neck dissection performed; ipsilateral neck dissection: patients who received ipsilateral neck dissection with or without contralateral neck dissection.

* = $p < 0.05$.

Koo et al reported a figure of 11% occult contralateral neck metastasis, and state that patients with clinically positive ipsilateral neck nodes also have a higher risk of contralateral neck occult metastasis.⁵ Kurita et al reported 14.7% contralateral neck metastasis,⁴ while Gonzalez-Garcia et al reported 9.8% ipsilateral and 4.4% contralateral neck recurrence.⁷ Lim et al reported 4% occult contralateral neck metastasis in early stage oral tongue SCC,⁶ and Koxalski et al reported 14% contralateral neck metastasis.³

The 5-year overall survival rate for the contralateral neck relapse group is 24.7%, while for the noncontralateral neck relapse group it is 61% ($p = 0.0001$). Koo et al also showed lower 5-year disease-specific and overall survival rates of OSCC patients with positive contralateral neck metastasis.⁵

There are a few reports in the literature with regard to the factors involved in the risk of contralateral metastasis. Koxalski et al reported that the clinical stage, tumor crossing of the midline, and floor of mouth involvement are predictors of contralateral metastasis, and give a figure of 14% contralateral neck metastasis.³ Kurita et al reported that the T stage, number of ipsilateral lymph node metastasis, and histopathologic grade are independent and significant predictors of contralateral neck metastasis.⁴ Gonzalez-Garcia et al showed that histopathologic grading and peritumor inflammation are statistically significantly related to contralateral neck recurrence.⁷ Lim et al reported no survival benefits of elective contralateral neck dissection for early-stage oral tongue SCC,⁶ while Hiratsuka et al reported that the mode of carcinoma invasion, intensity of lymphocytic infiltration, degree of differentiation, number of mitotic figures, and type of growth are predictors of occult neck lymph node metastasis.² Godden et al reported that tumor thickness of more than 5 mm is a strong predictor for neck recurrence of OSCC,¹ while Koo et al reported that advanced ($\geq T3$) OSCC, midline-crossing tumor, and positive ipsilateral neck node have higher risks of contralateral occult neck metastasis.⁵

From the data here, midline-crossing tumor ($p = 0.0208$) and mouth floor invasion ($p = 0.0196$) are significantly related to the presence of cN2c and pN2c. This is consistent with other studies.^{3,5} All pN2c patients were histopathologic and had clinically advanced tumor stage ($\geq T3$), which shows statistically significant ($p = 0.0235$) correlation to N2c by univariate analysis, although not by multivariate analysis. This result is similar to those reported previously.^{4,5} For clinical practice, our study further reinforces the predictive value of midline-crossing tumor, mouth floor invasion tumor, and advanced tumor stage ($\geq T3$). Therefore, prophylactic contralateral neck dissection is highly recommended for these patients.

The other part of our study focused on contralateral neck relapse after treatment. Because contralateral neck dissection remains controversial, the patients were grouped according to neck dissection performance. Among the 26 contralateral neck relapse patients, only one came from the primary contralateral neck dissection group. Eighteen were from the ipsilateral neck dissection group and seven came from the non-neck dissection group. For patients who had undergone contralateral neck dissection with either prophylactic or curative intent, poorly differentiated tumors were statistically significant having contralateral neck relapse. For those patients who had undergone ipsilateral neck dissection, mouth floor invasion ($p = 0.0025$) and tumor differentiation ($p = 0.0228$) showed statistical significance for contralateral neck relapse.

From the above description, prophylactic contralateral neck dissection actually reduced the risk of contralateral neck failure of OSCC. Prophylactic contralateral neck dissection is therefore suggested for primary oral tumors with mouth floor invasion or midline crossing, or at advanced tumor stage ($\geq T3$). Adjuvant therapy such as radiotherapy for the contralateral neck region is an alternative for clinicians if there is tumor invasion of the mouth floor or if the tumor is poorly differentiated.

7. Conclusions

Contralateral neck metastasis is a critical factor influencing the survival of patients with OSCC. The contralateral side of the neck is a potentially preventable site of recurrence in tumors of the oral cavity. This study shows that prophylactic contralateral neck dissection is recommended for oral cancer with the presence of midline crossing and mouth floor invasion. Adjuvant therapy on the contralateral side of the neck is suggested for poorly differentiated tumors or if there is mouth floor tumor invasion or tumor with midline crossing.

References

1. Godden DR, Ribeiro NF, Hassanein K, Langton SG. Recurrent neck disease in oral cancer. *J Oral Maxillofac Surg.* 2002;60: 748–753. discussion 753–755.
2. Hiratsuka H, Miyakawa A, Nakamori K, Kido Y, Sunakawa H, Kohoma G. Multivariate analysis of occult lymph node metastasis as a prognostic indicator for patients with squamous cell carcinoma of the oral cavity. *Cancer.* 1997;80:351–356.
3. Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR. Factors influencing contralateral lymph node metastasis from oral carcinoma. *Head Neck.* 1999;21:104–110.
4. Kurita H, Koike T, Narikawa JN, et al. Clinical predictors for contralateral neck lymph node metastasis from unilateral squamous cell carcinoma in the oral cavity. *Oral Oncol.* 2004;40:898–903.
5. Koo BS, Lim YC, Lee JS, Choi EC. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. *Head Neck.* 2006;28:896–901.
6. Lim YC, Lee JS, Koo BS, Kim SH, Kim YH, Choi EC. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. *Laryngoscope.* 2006;116:461–465.
7. González-García R, Naval-Gas L, Sastre-Pérez J, et al. Contralateral lymph neck node metastasis of primary squamous cell carcinoma of the tongue: a retrospective analytic study of 203 patients. *Int J Oral Maxillofac Surg.* 2007;36:507–513.
8. Woolgar JA. The topography of cervical lymph node metastases revisited: the histological findings in 526 sides of neck dissection from 439 previously untreated patients. *Int J Oral Maxillofac Surg.* 2007;36:219–225.